CGM Metrics Predict Imminent Progression to Type 1 Diabetes: Autoimmunity Screening for Kids (ASK) Study

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OBJECTIVE

Children identified with stage 1 type 1 diabetes are at high risk for progressing to stage 3 (clinical) diabetes and require accurate monitoring. Our aim was to establish continuous glucose monitoring (CGM) metrics that could predict imminent progression to diabetes.

RESEARCH DESIGN AND METHODS

In the Autoimmunity Screening for Kids study, 91 children who were persistently islet autoantibody positive (median age 11.5 years; 48% non-Hispanic White; 57% female) with a baseline CGM were followed for development of diabetes for a median of 6 (range 0.2–34) months. Of these, 16 (18%) progressed to clinical diabetes in a median of 4.5 (range 0.4–29) months.

RESULTS

Compared with children who did not progress to clinical diabetes (nonprogressors), those who did (progressors) had significantly higher average sensor glucose levels (119 vs. 105 mg/dL, $P < 0.001$) and increased glycemic variability (SD 27 vs. 16, coefficient of variation, 21 vs. 15, mean of daily differences 24 vs. 16, and mean amplitude of glycemic excursions 43 vs. 26, all $P < 0.001$). For progressors, 21% of the time was spent with glucose levels >140 mg/dL (TA140) and 8% of time >160 mg/dL, compared with 3% and 1%, respectively, for nonprogressors. In survival analyses, the risk of progression to diabetes in 1 year was 80% in those with TA140 >10%; in contrast, it was only 5% in the other participants. Performance of prediction by receiver operating curve analyses showed area under the curve of ≥0.89 for both individual and combined CGM metric models.

CONCLUSIONS

TA140 >10% is associated with a high risk of progression to clinical diabetes within the next year in autoantibody-positive children. CGM should be included in the ongoing monitoring of high-risk children and could be used as potential entry criterion for prevention trials.

Children who are identified through population screening to have multiple islet autoantibodies (stage 1 type 1 diabetes) are at high risk for developing clinical type 1 diabetes (stage 3 type 1 diabetes) (1,2). Through TrialNet and other studies (3,4), it is known that among individuals with positive islet autoantibodies, there is a

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**A complete list of the ASK Study Group members can be found in the supplementary material online.*

period of impaired fasting glucose (100–125 mg/dL) or impaired glucose tolerance (oral glucose tolerance, 2-h glucose 140–199 mg/dL) preceding type 1 diabetes onset by several months or years.

In addition, early diagnosis of type 1 diabetes without diabetic ketoacidosis (DKA) is associated with long-term benefits, including better HbA_{1c}, which, in turn, is associated with fewer diabetes complications (5,6). As prevention, or at least delay, of type 1 diabetes from stage 2 to stage 3 becomes a reality (7), it is critical to have accurate tools to identify this dysglycemic period and implement early treatment at the right time to preserve endogenous insulin secretion. Thus, children with islet autoantibodies who are presymptomatic require accurate and close surveillance for prediction of their progression through the different stages of type 1 diabetes, described by a joint statement from the American Diabetes Association (ADA), JDRF, and the Endocrine Society in 2015 (2).

Although the 2018 International Society for Pediatric and Adolescent Diabetes guidelines do not recommend antibody screening outside of defined research studies (8), the current ADA guidelines recommend screening for islet autoantibodies in the setting of a research trial or outside of research for first-degree family members of a proband with type 1 diabetes. The ADA guidelines further highlight that persistence of autoantibodies is a risk factor for clinical diabetes and may be an indication for intervention in the setting of a clinical trial (9).

In the United States, the JDRF has launched a nationwide clinical islet autoantibody screening initiative, called T1Detect, for the general population. Individuals and their families have the option to forward the results to a clinician when signing up for testing online. Individuals found to be autoantibody positive will need to be monitored for progression to diabetes to avoid DKA and for eligibility for clinical trials of potential therapies to preserve endogenous insulin secretion.

The Autoimmunity Screening for Kids (ASK) study is a clinical research study in which Colorado children ages 1–17 years are screened for islet and celiac autoantibodies. The DKA rate in the ASK study is ~6% whereas the DKA rate in 2020 in Colorado was 62% (10). Islet autoantibody screening in ASK has been shown to be cost-effective if it decreases the rate of DKA by 20% (i.e., from 40% to 32%) and subsequently lowers the HbA_{1c} by 0.1% (1 mmol/mol) (11). DKA at diagnosis of type 1 diabetes in children has been associated with poor long-term glycemic control, with HbA_{1c} levels remaining 0.3–1.0% higher than in those diagnosed without DKA (5). In addition to benefits of improved metabolic status at diagnosis, there are potential interventions on the horizon for early-stage type 1 diabetes. The first positive trial with teplizumab showed delay of onset of type 1 diabetes by 2–3 years in relatives with stage 2 disease (7,12).

The current standard surveillance methods for presymptomatic type 1 diabetes are a 2-h oral glucose tolerance test (OGTT) and an HbA_{1c} test every 6 months. Although OGTT measures predict progression through the stages of type 1 diabetes across different populations and have value as entry criteria for prevention trials (3,13,14), there are important challenges to the use of OGTT in clinical care. These barriers include significant day-to-day variability and poor acceptance by children and their families due to time constraints and intravenous access requirement. Some of the OGTT variability in autoantibody-positive populations is likely attributable to fluctuations that are part of the nature of the disease. The Environmental Determinants of Diabetes in the Young (TEDDY) study has shown that OGTTs are not a major contributor of type 1 diabetes diagnosis in the very young, with only 6% of children younger than 3 years being diagnosed by OGTT (15). HbA_{1c} testing is highly specific for diabetes diagnosis but has limited sensitivity in children, especially in the very young (16,17).

Importantly, continuous glucose monitoring (CGM) detects glucose abnormalities before diagnosis of type 1 diabetes in children with positive islet autoantibodies, although the number of participants in these previous studies was small (18–20). In the Diabetes Autoimmunity Study in the Young (DAISY), ≥18% CGM time spent at >140 mg/dL (TA140; 7.8 mmol/L) predicts progression to diabetes in autoantibody-positive children (18,21). Development of CGM-derived measures of evolving dysglycemia will allow for a more accurate and well-tolerated method of monitoring progression through the stages of type 1 diabetes, compared with OGTTs. The aim of the present study was to identify and assess various CGM metrics for their accuracy in predicting imminent progression to stage 3 clinical diabetes among children in the general population found to be at high risk for diabetes.

RESEARCH DESIGN AND METHODS

Study Population

Since January 2017 and until 1 December 2019, the ASK study has screened 22,566 Colorado children ages 1–17 years for islet and celiac autoantibodies at private pediatric practices, community clinics, and the Children's Hospital Colorado and its satellite locations. Children who screen positive for any of the autoantibodies at the initial screening are invited to the Barbara Davis Center for Diabetes, University of Colorado School of Medicine, Aurora, for a confirmation visit within 3 months of screening. Children who persistently test positive for ≥1 islet autoantibody at confirmation are invited to participate in the monitoring follow-up program at the Barbara Davis Center within 3–6 months of confirmation visit, with HbA_{1c} testing every 3–6 months. Families receive education on diabetes symptoms and home blood-glucose testing. Children who are confirmed positive for multiple islet autoantibodies, confirmed positive for a single autoantibody by both assays (radiobinding [RBA] and electrochemiluminescence [ECL]), or have an HbA_{1c} ≥6% (42 mmol/mol) are also offered optional OGTTs and CGM every 6 months after the baseline monitoring visit. The overall ASK screening and monitoring program flowchart is shown in the Supplementary Figure. As of 1 September 2020, 158 children were eligible for CGMs and OGTTs. Of these, 94 children completed initial CGM and 50 completed an initial OGTT. Diagnosis of diabetes was defined according to ADA criteria (9). Informed consent was obtained from the parents of each study participant. The Colorado Multiple Institutional Review Board approved all study protocols.

Autoantibody Assays

Autoantibodies to insulin, GAD, IA2, and ZnT8 were measured in the Immunogenetics Laboratory at the Barbara Davis Center using previously described RBA assays and high-affinity ECL assays (22–25). In the 2020 Islet

Autoantibody Standardization Program Workshop, sensitivities and specificities, respectively, for the RBA among patients newly diagnosed with type 1 diabetes were 62% and 99% for micro-insulin autoantibody; 78% and 99% for GAD antibody; 72% and 100% for IA-2 antibody; and 74% and 100% for ZnT8. In the 2020 Islet Autoantibody Standardization Program Workshop, sensitivities and specificities, respectively, for ECL were 66% and 99% for insulin autoantibody, 78% and 100% for GAD antibody, and 72% and 100% for IA-2 antibody.

CGM

Participants were asked to complete a 7–10 day period of CGM wear with the Dexcom G4 with 505 software (before April 2019) or Dexcom G6 (after April 2019). For the Dexcom G4, participants were instructed not to use acetaminophen 1 day before and during the time of CGM wear and were given a meter for blood glucose calibrations twice a day (One Touch Ultra [LifeScan Inc., a Johnson and Johnson subsidiary, Milpitas, CA] before June 2018; and Contour Next One [Ascensia Diabetes Care, Parsippany, NJ]) after June 2018). Participants were blinded to real-time CGM readings, and a study physician (a pediatric endocrinologist) reviewed the CGM results when monitoring was completed.

Statistical Analysis

Statistical analyses were performed using SAS software, version 9.4, and GraphPad Prism, version 9.02. Categorical variables were analyzed using Pearson χ^2 tests. Continuous variables were tested using the *t* test for differences in means or the Wilcoxon rank-sum test for differences in medians. The first 12 h of CGM data were removed from the analyses. If >20% of the data were missing on any given day, the data for that day were also excluded. Only CGM records with ≥96 h of data were included. Of the 94 participants completing initial CGM, three sets of CGM data were excluded from analyses because <96 h of data were available with a total of 91 participants included in all analyses. After data clean-up, CGM data were limited to the first 96 h of available data for all participants for the analyses to be consistent. Measures of glycemic control included HbA_{1c} (DCA Vantage Siemens, Bayer Corp., Elkhart, IN), overall sensor glucose values, percent time above various sensor glucose cutoffs as well as area under the curve (AUC) of glucose calculated by the trapezoidal rule. Primary variables to characterize glycemic variability included glucose range, the overall SD, the coefficient of variation (CV), the mean of daily differences (MODD) and the mean amplitude of glycemic excursions (MAGE). Receiver operating characteristic (ROC) curves were generated to compare the AUC of different CGM metrics for type 1 diabetes prediction (26). The ROC curves were constructed by plotting the false-positive rate (1 − specificity) on the *x*-axis and the true-positive rate (sensitivity) rate on the *y*-axis for all possible binary thresholds for the CGM metrics (26). The ROC curve allowed us to identify a cutoff that maximized the sum of sensitivity and specificity (27). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for diabetes prediction were calculated for the optimal CGM metric cutoffs. Cox proportional hazards models were used to estimate the risk of type 1 diabetes for various CGM metrics. Follow-up time was defined as time between baseline CGM and diabetes onset for those who progressed to clinical diabetes or last visit for those who did not progress to diabetes. Dot-plot charts for these same CGM metrics were performed between children who progressed to clinical diabetes (progressors) and those who did not (nonprogressors). A 2-tailed *P* value with an α level for significance was set at 0.05.

RESULTS

A total of 91 children positive for islet autoantibody and with a baseline CGM were followed for development of type 1 diabetes for a median of 6 (interquartile range 1.0–10.8; range 0.2–34) months. Of these, 16 (18%) progressed to diabetes in a median of 4.5 (interquartile range 0.9–9.7; range 0.4–29) months. The baseline characteristics of study participants are shown in Supplementary Table 1. Age, sex, ethnicity, and BMI were similar between islet autoantibody–positive participants who progressed to diabetes and those who did not progress to diabetes. Baseline HbA_{1c} was higher in progressors than in nonprogressors (respectively, 5.6% vs. 5.2% [38 vs. 33 mmol/mol]; $P = 0.005$). OGTT data at baseline were only available for 17 participants.

Baseline CGM measures of glycemic control and variability are summarized in Supplementary Table 2. Compared with nonprogressors, participants progressing to diabetes had significantly increased glycemic variability (median SD 27 vs. 16 mg/dL [1.5 vs. 0.9 mmol/L]; CV 21% vs. 15%; MAGE 43 vs. 26 [2.4 vs. 1.4 mmol/L]; MODD 24 vs. 16 [1.3 vs. 0.9 mmol/L]; all $P < 0.001$) as well as higher sensor average (median 119 vs. 105 mg/dL [6.6 vs. 5.8 mmol/L]; $P < 0.001$). Progressors spent 21% of time above 140 mg/dL (TA140; 7.8 mmol/L) and 8% of time >160 mg/dL (TA160; 8.9 mmol/L) compared with, respectively, 3% and 1% for nonprogressors ($P < 0.0001$). The AUC values of glucose overall, during the day and at night, also were significantly different between progressors and nonprogressors (all $P \leq 0.03$).

ROC curves were generated to compare the AUC of different CGM metrics and HbA_{1c} for type 1 diabetes prediction. Performance of type 1 diabetes prediction by ROC analyses showed an AUC of ≥0.89 for both individual CGM variables such as TA140, SD, and MAGE, as well as several combined CGM metric models (all $P < 0.0001$) (Table 1).

Sensitivity, specificity, PPV, and NPV for diabetes prediction were calculated for different CGM metrics and HbA_{1c}. The cutoffs of 10% TA140 had 91% specificity and 97% NPV, with 67% PPV and 88% sensitivity for diabetes prediction (Table 2). TA140 >15% had 99% specificity and 94% NPV with 92% PPV and 69% sensitivity for diabetes prediction.

Cox proportional hazards models were performed for those individual CGM metrics with AUC of ≥0.88 for diabetes prediction by ROC analyses. The risk of progression to type 1 diabetes in 1 year was 80% in those with TA140 >10%; in contrast, it was only 5% in participants with TA140 ≤10% ($P < 0.0001$) (Fig. 1*A*). Similarly, the risk of progression to diabetes in 1 year was 73% vs. 7% in those with TA160 >3.5% vs. ≤3.5%, respectively ($P < 0.0001$) (Fig. 1*B*), whereas the risk of progression to diabetes in 1 year was 83% vs. 9% in those with >1.9% vs. ≤1.9% time spent >180 mg/dL (TA180; 10 mmol/L), respectively ($P < 0.0001$) (Fig. 1*C*). Survival curves by MAGE >37 vs. ≤37 showed risk of progression to

Table 1—Receiver operating characteristic analyses for prediction of type 1 diabetes

Variable	AUC (95% CI)	*P* value
HbA_{1c}	0.75 (0.57–0.93)	0.006
% time > 120 mg/dL (6.7 mmol/L)	0.81 (0.66–0.96)	<0.0001
% time > 140 mg/dL (7.8 mmol/L)	0.89 (0.75–1.00)	<0.0001
% time > 160 mg/dL (8.9 mmol/L)	0.88 (0.74–1.00)	<0.0001
% time > 180 mg/dL (10 mmol/L)	0.88 (0.76–0.99)	<0.0001
% time > 200 mg/dL (11.1 mmol/L)	0.81 (0.68–0.94)	<0.0001
SD	0.89 (0.79–0.98)	<0.0001
CV	0.84 (0.74–0.93)	<0.0001
MAGE	0.90 (0.82–0.99)	<0.0001
MODD	0.86 (0.75–0.97)	<0.0001
% time > 140 mg/dL (7.8 mmol/L) and SD	0.90 (0.77–1.00)	<0.0001
% time > 140 mg/dL (7.8 mmol/L) and CV	0.91 (0.79–1.00)	<0.0001
% time > 140 mg/dL (7.8 mmol/L) and MAGE	0.91 (0.79–1.00)	<0.0001
% time > 160 mg/dL (8.9 mmol/L) and SD	0.90 (0.78–1.00)	<0.0001
% time > 160 mg/dL (8.9 mmol/L) and CV	0.91 (0.80–1.00)	<0.0001
% time > 160 mg/dL (8.9 mmol/L) and MAGE	0.91 (0.80–1.00)	<0.0001
% time > 180 mg/dL (10 mmol/L) and SD	0.90 (0.80–1.00)	<0.0001
% time > 180 mg/dL (10 mmol/L) and CV	0.90 (0.81–0.99)	<0.0001
% time > 180 mg/dL (10 mmol/L) and MAGE	0.92 (0.83–1.00)	<0.0001
SD and CV	0.88 (0.75–1.00)	<0.0001
SD and MAGE	0.91 (0.82–1.00)	<0.0001
CV and MAGE	0.90 (0.82–0.99)	<0.0001

AUC, area under the curve; CV, coefficient of variation; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences.

type 1 diabetes in 1 year of 64% vs. 12% ($P < 0.0001$) (Fig. 1*E*), and survival curves by SD >20 vs. ≤20 showed risk of progression to diabetes in 1 year of 60% vs. 6%, respectively ($P < 0.0001$) (Fig. 1*D*).

Figure 2 shows dot-plot charts for progressors and nonprogressors for these same CGM metrics with AUC of ≥0.88. TA140 (Fig. 2*A*), TA160 (Fig. 2*B*) and TA180 (Fig. 2*C*) were all significantly higher in the progressors than in the nonprogressors (all $P < 0.0001$). Increased CGM variation characterized by MAGE (Fig. 2*E*) and SD (Fig. 2*D*) was observed in progressors compared with nonprogressors (all $P < 0.0001$).

CONCLUSIONS

To our knowledge, this is the largest prospective study to date to analyze CGM metrics as predictors of progression to type 1 diabetes in autoantibody-positive children identified through general population screening. Several small studies have reported pilot CGM data prior to diabetes onset in participants at risk for developing type 1 diabetes (18–21). Of 91 children who were persistently islet autoantibody positive and followed in this study, we found that various CGM metrics, both individual and combined CGM variables, accurately predicted progression to stage 3 diabetes within 12 months. Individual CGM metrics such as TA140 are readily available on a CGM download without complex calculations and, therefore, can be used for monitoring participants at risk for type 1 diabetes and as potential entry criteria or end point for prevention trials. We propose TA140 >10% as a new criterion for dysglycemia (stage 2 type 1 diabetes) with a high risk of progression to clinical diabetes within the next 12 months in autoantibody-positive children.

Previous studies have reported that CGM can detect early hyperglycemia in autoantibody-positive children at risk for progression to type 1 diabetes; however, these studies were all relatively small and included <25 participants (18–21). In the prospective DAISY study, ≥18% CGM at TA140 predicts progression to diabetes in autoantibody-positive children (mean age 15.7 years) (21). In the Type 1 Diabetes Prediction and Prevention Study, which included 10 multiple islet autoantibody–positive children and 10 age-matched children as autoantibody-negative controls (mean age 10 years) (20), the autoantibody–positive children had higher mean values and higher variation in glucose levels during CGM than did the control group (with TA140 mg/dL of 5.8% in the case children compared with 0.4% in the control group; $P = 0.04$). In the Belgian Diabetes Registry, 22 antibody-positive relatives of patients with type 1 diabetes (mean age

Table 2—Sensitivity, Specificity, PPV, and NPV for HbA_{1c} and different CGM metrics

Model Source	Cutoff	Sensitivity	Specificity	PPV	NPV
HbA_{1c}	5.5 (37 mmol/mol)	43.8	89.3	46.7	88.2
% time > 120 mg/dL (6.7 mmol/L)	37.3	68.8	94.7	73.3	93.4
% time > 140 mg/dL* (7.8 mmol/L)	10	87.5	90.7	66.7	97.1
% time > 140 mg/dL* (7.8 mmol/L)	15	68.8	98.7	91.7	93.7
% time > 160 mg/dL (8.9 mmol/L)	3.5	81.3	90.7	65.0	95.8
% time > 180 mg/dL (10 mmol/L)	1.9	68.8	96.0	78.6	93.5
% time > 200 mg/dL (11.1 mmol/L)	0.3	62.5	94.7	71.4	92.2
SD	20	81.3	81.3	48.2	95.3
CV	16	81.3	65.3	33.3	94.2
MAGE	37	68.8	90.7	61.1	93.2
MODD	19	75.0	80.0	44.4	93.8

Data reported as percentages unless otherwise indicated. *The cutoff from receiver operator curve for percentage of time ≥140 mg/dL was 10.5%, which had the same sensitivity, specificity, PPV, and NPV as 10% of time at ≥140 mg/dL. CV, coefficient of variation; MAGE, mean amplitude of glycemic excursions; MODD, mean of daily differences; NPV, negative predictive value; PPV, positive predictive value.

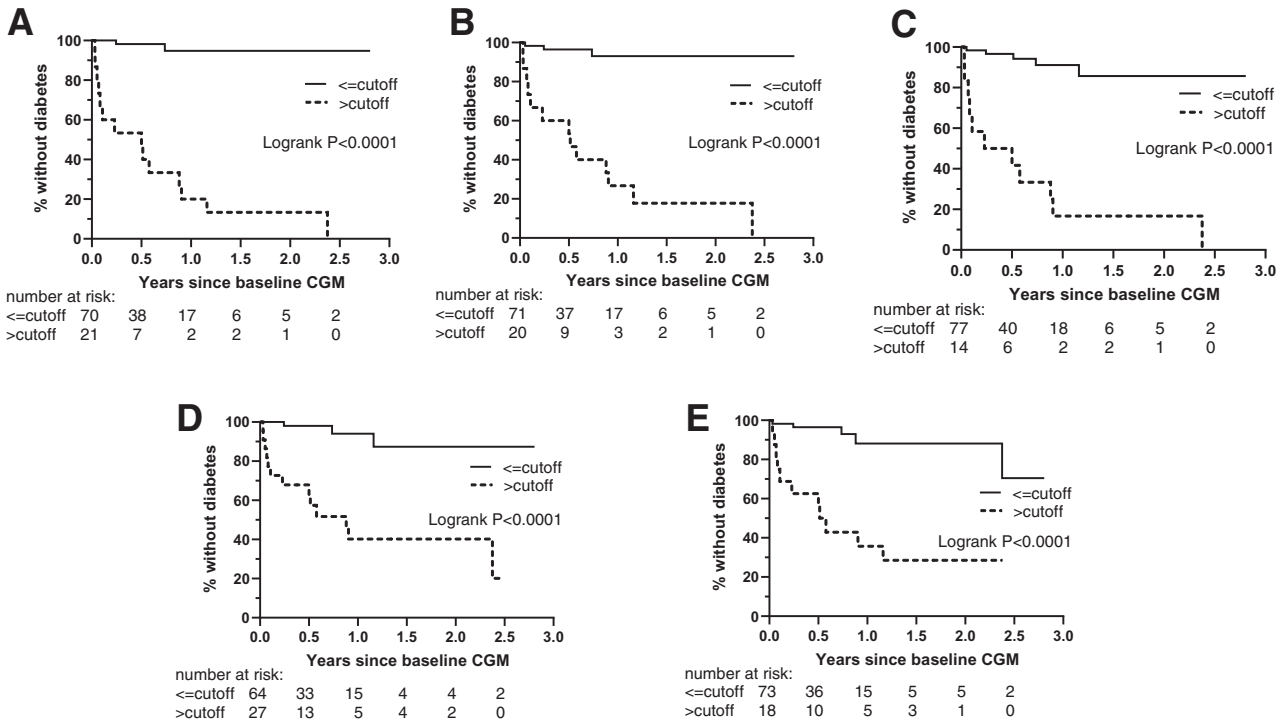

Figure 1—Development of diabetes by various CGM metrics. *A*: Time spent >140 mg/dL (7.8 mmol/L) with cutoff >10% vs. ≤10%; *B*: time spent >160 mg/dL (8.9 mmol/L) with cutoff >3.5% vs. ≤3.5%; *C*: time spent >180 mg/dL (10 mmol/L) with cutoff >1.9 vs. ≤1.9%; *D*: SD with cutoff >20 vs. ≤20; and *E*: mean amplitude of glycemic excursions (MAGE) with cutoff >37 vs ≤37. Survival analysis was performed for the development of diabetes since baseline CGM. Follow-up time was defined as time between baseline CGM and diabetes onset for those who progressed to clinical diabetes or last visit for those who did not progress to diabetes.

19 years) had a CGM, a hyperglycemic clamp test, and an OGTT (19); CGM-derived glycemic variability measures and the glucose disposal rate better discriminated these normoglycemic relatives with impending dysglycemia or diabetes than did self-monitoring of blood glucose and AUC C-peptide.

In this study of 91 antibody-positive children from the general population (median age 11.5 years), we report that both individual and combined CGM

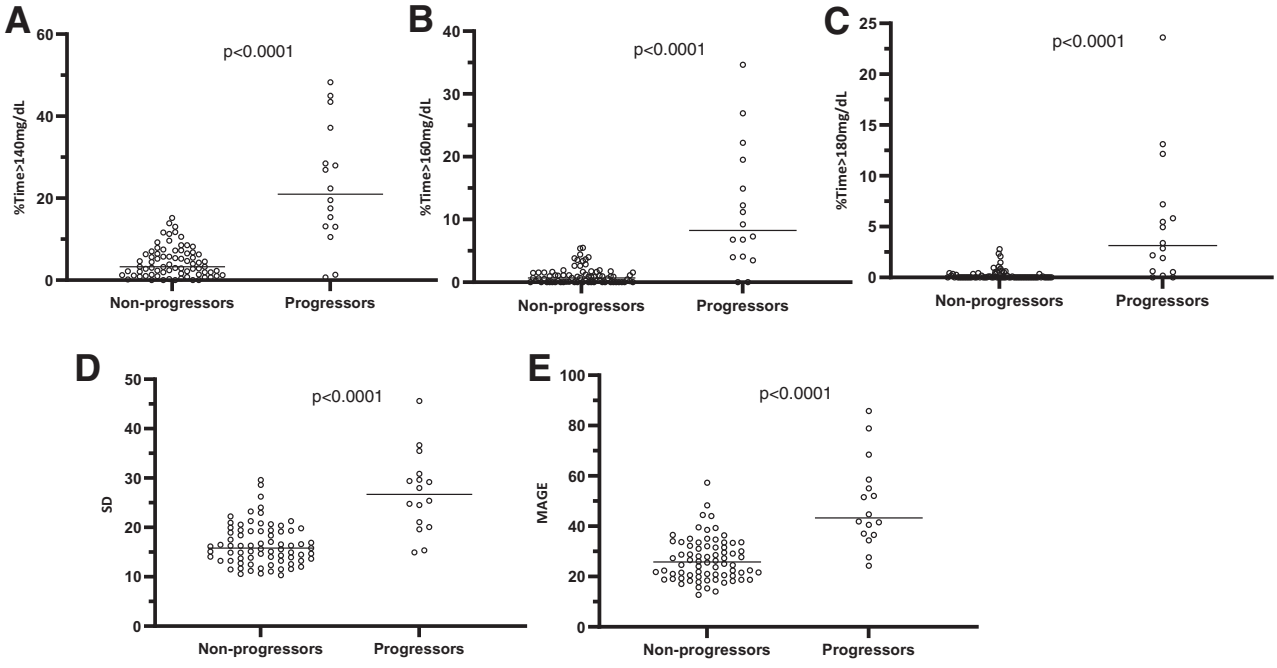

Figure 2—Dot-plot charts for various CGM metrics between progressors and nonprogressors. *A*: time spent >140 mg/dL (7.8 mmol/L); *B*: time spent >160 mg/dL (8.9 mmol/L); *C*: time spent >180 mg/dL (10 mmol/L); *D*: SD; and *E*: mean amplitude of glycemic excursions (MAGE).

metrics can accurately predict progression to stage 3 type 1 diabetes within the next year. Individual CGM metrics with AUC of ≥0.88 for diabetes prediction by ROC analyses include TA140, TA160, TA180, MAGE, and SD. Although various CGM metrics are excellent predictors, individual CGM metrics such as TA140 are graphically available on a CGM download and can be easily explained to participants and their families. Therefore, we propose TA140 >10% as a new criterion for dysglycemia (stage 2 type 1 diabetes) with a high risk of progression to clinical diabetes within the next year in autoantibody-positive children. In this study, the risk of progression to type 1 diabetes in 1 year was 80% in those with TA140 >10% compared with only 5% in participants with TA140 ≤10%. Although TA140 >10% had better sensitivity regarding diabetes prediction, TA140 >15% had the best specificity. Because the current follow-up in this study is short (median 6 months), we propose TA140 >15% as marker of imminent progression to clinical diabetes (i.e., within the next 6 months). Differences in cutoff values for CGM TA140 found in previous studies (18–21) could be due to small numbers of participants, differences in age of the participants, as well as a variety of sensors used due to availability of new technology over time.

Although OGTTs and their associated measures, including glucose, C-peptide, and various combined metabolic measures, risk scores and index (e.g., Diabetes Prevention Trial-Type 1 Risk Score [DPTRS], DPTRS60, Index60) can accurately predict progression to diabetes in high-risk participants (28–33), other measures of risk and progression to diabetes are needed because screening efforts (including the Fr1da Study, ASK Study, PrIMeD Study) are underway in the general population in several countries (11,34,35). Awareness of risk alone does not prevent progression to severe metabolic decompensation at the time of diagnosis (16). Children found to be autoantibody positive in general population screening will need to be monitored closely for progression to diabetes and to avoid DKA at diabetes onset. Current CGM devices, which do not need any calibration, are well accepted by children and their parents for monitoring diabetes risk and progression. They offer an accurate and nearly instantaneous measure of sensor glucose pattern for a participant over a few days in the real home environment.

In a CGM study combining antibody-positive children from DAISY, youth with cystic fibrosis (CF) from the Glycemic Monitoring in Cystic Fibrosis Study and overweight or obese youth with BMI ≥85th percentile at risk for type 2 diabetes, we reported that HbA_{1c} may be normal, despite hyperglycemia and increased glycemic variability, not only in individuals with CF but also in autoantibody-positive individuals at risk for type 1 diabetes (36). In the present study, HbA_{1c} at baseline was highly specific (89%) but not sensitive (44%) for type 1 diabetes prediction, which is consistent with findings of previous studies (16,17). Measures of glycemic variability measured by CGM, such as SD, as well as TA140 are accurate measures of rapid progression to diabetes and, therefore, should be included in the ongoing monitoring of at-risk participants. In addition, these CGM metrics could be useful as potential entry criteria and end points for prevention trials and should be included in clinical trials for further evaluation.

There are currently no guidelines for monitoring participants at increased risk for type 1 diabetes. Most education and monitoring of individuals with presymptomatic type 1 diabetes is done through clinical research studies. Participants monitored in these studies may be diagnosed early using OGTT; however, only 6% of children younger than 3 years are diagnosed by OGTT (15). Although HbA_{1c} is easily measured in clinic, OGTTs are time consuming and unlikely to become part of routine diabetes monitoring. In our experience, CGM has been well accepted by families. We propose that CGM could be done every 3–12 months, depending on the stage of type 1 diabetes and the age of the participant, although the optimal frequency of monitoring still needs to be further evaluated by examination of serial measurements. Although parents of children confirmed to be autoantibody positive often have increased anxiety (37,38), those children at risk for type 1 diabetes who previously enrolled in research monitoring have also been shown to have improved diabetes-related quality of life and a lower level of parenting stress postdiagnosis, compared with children diagnosed in the community (39). In the ASK study (40), in families enrolled in monitoring, accuracy of risk perception was low and parental anxiety after learning of a child's positive screening result decreased rapidly over initial visits. Additional research and potential tailored interventions are needed regarding both accuracy of risk perception and parental anxiety as part of current, ongoing general population screening programs.

Limitations of this study include a relatively short follow-up overall and a small number of participants completing both CGM and OGTTs at the same time, because both of these are optional procedures in the ASK study. Therefore, we were not able to directly compare the prediction accuracy of CGM versus OGTT measures. In addition, in this study, we combined data from both the Dexcom G4, which requires calibrations, and the Dexcom G6, which does not require any calibration. As ASK and other studies (e.g., TrialNet, Precision Individualized Medicine in Diabetes Study [PrIMeD]) continue to offer CGM and monitor participants at risk for developing stage 3 type 1 diabetes, it will be possible to use CGM data to provide longer-term risk estimates for the various stages of type 1 diabetes as well as determine intermediate end points for type 1 diabetes clinical trials (41). Although the ASK study has not been collecting information on satisfaction regarding CGMs, more eligible participants and their families chose to complete a CGM (n = 94 participants) than an OGTT (n = 50 participants). Finally, the current follow-up duration in the ASK study is relatively short, and the accuracy of these CGM metrics will need to be validated in other populations.

In conclusion, this is the largest prospective study to date analyzing CGM data from 91 autoantibody-positive children from the general population. CGM has multiple advantages over previous modalities and should be included in the ongoing monitoring of high-risk children. In particular, TA140 >10% is associated with a high risk of progression to clinical diabetes within the next year in autoantibody-positive children. More studies are needed to determine useful CGM metrics for entry criteria and end points for clinical prevention trials.

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